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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,926	05/03/2007	Barbara Ensoli	114-06	7925

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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,926	ENSOLI, BARBARA	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-50,52-56 and 63-67* is/are pending in the application.

4a) Of the above claim(s) *53-56 and 65-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-50,52,63 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/2009 & 2/22/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

It is noted that claims 53-56 and 65-67 are withdrawn. However, these claims do not recite the correct status identifiers in the listing of claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 37-50, 52, 63 and 64 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to, *inter alia*, peptides that are fragments, mutants or variants thereof.

The written description rejection is made because the claims are interpreted as being drawn to a genus of peptides recited as " fragments, mutants or variants thereof." The applicable standard for the written description requirement can be found in MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written

Description Guidelines; Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004). To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is SEQ ID NOs:1 and 2 and the structure/function of the polypeptides (capable of binding). There is no disclosure of any particular portion of the structure that must be conserved (or changed/mutated) in order to be " fragments, mutants or variants thereof." Further, the specification does not provide guidance for creating mutants or variants. Without proper guidance from the specification, one of ordinary skill in the art would not know where to mutate the proteins or how to create a variant of the protein.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The court clearly states in Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to

recognize that the inventors invented what is claimed. As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of "fragments, mutants or variants thereof." Given that the specification has only described the structure and function of SEQ ID NOs:1 and 2, the full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph.

Response to Arguments

In the reply dated October 13, 2009, applicants argue that there is both structural and functional language in the claims which clearly establish that the inventors possessed the invention as of the filing date. Applicants' arguments have been fully considered but are not found persuasive.

Although HIV Tat, the residues comprising the V3 region of gp120 and the V3 binding region of Tat are known in the art, applicants have not provided any guidance as to which residues or portions of the Tat binding region can be changed or mutated to produce variants or mutants. Further, applicants have not provided any guidance as to which residues of the Tat binding region cannot be changed or mutated such that the binding function is maintained. Further, the specification does not provide guidance for creating mutants or variants. Without proper guidance from the specification, one of ordinary skill in the art would not know where to mutate the Tat proteins or how to create a variant of the Tat protein. While one would be able to construct variants and mutants of Tat and test them for their ability to bind V3, this process of guesswork does not put one in possession of the genus of polypeptides.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35, 37-50, 52, 63 and 64 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Several of the claims recite "fragment, mutant or variant thereof." These terms are not defined in a manner such that one skilled in the art would know the scope of the claims. One would not know what type of "fragment, mutant or variant thereof" are encompassed by the claims or if a particular "fragment, mutant or variant thereof" would be immunogenic or would be capable of binding the specified residues of SEQ ID NO:1 or 2. One of ordinary skill in the art would not know the metes and bounds of the claims.

Response to Arguments

In the reply dated October 13, 2009, applicants argue that there is both structural and functional language in the claims which now renders the phrase "fragment, mutant or variant thereof" definite. Applicants' arguments have been fully considered but are not found persuasive.

Although HIV Tat, the residues comprising the V3 region of gp120 and the V3 binding region of Tat are known in the art, applicants have not provided any guidance as to which residues or portions of the Tat binding region can be changed or mutated to produce variants or mutants. Further, applicants have not provided any guidance as to

which residues of the Tat binding region cannot be changed or mutated such that the binding function is maintained. Further, the specification does not provide guidance for creating mutants or variants. Without proper guidance from the specification, one of ordinary skill in the art would not know where to mutate the Tat proteins or how to create a variant of the Tat protein. Therefore, one skilled in the art would know the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-40, 42, 45, 50, 51, 63 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Voss et al. (WO 01/54719).

The claims are directed to a complex comprising first and second peptides, the first peptide comprising the V3 loop of gp120, and wherein the V3 loop is bound to a binding region on the second peptide, the binding region on the second peptide comprising at least residues 21-40 and 46-58 of the Tat protein set forth in SEQ ID NO:1, or a fragment, mutant or variant thereof capable of binding a region on gp120 comprising residues 301-419 of SEQ ID NO:2.

According to page 5 of the specification, the "complex of the present invention may generally be suitably provided as a combination of two peptide species in a vehicle

suitable for injection. . . . The complex of the present invention will typically comprise the two peptide species in contact with each other. Whilst it is preferred, it is not necessary that the two species be present in stoichiometric amounts, nor that even a majority of either species be complexed or bound to the other. All that is required is that a sufficient amount of an antigenic combination of the two species be presented in order to be able to stimulate an immune response there against."

Voss et al. discloses the use of an HIV Tat protein and an HIV gp120 protein in the manufacture of a vaccine for immunization against HIV (abstract). In accordance with the teaching in the specification, Voss et al. discloses a combination of the two proteins. Voss also discloses a kit comprising one or more of gp120, Nef and Tat proteins (see page 12). Thus, Voss et al. anticipates the claimed invention.

Claims 35-40, 42, 45, 50, 51 and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Voss et al. (Journal of Virology, 2003, 77(2):1049-1058).

According to page 5 of the specification, the "complex of the present invention may generally be suitably provided as a combination of two peptide species in a vehicle suitable for injection. . . . The complex of the present invention will typically comprise the two peptide species in contact with each other. Whilst it is preferred, it is not necessary that the two species be present in stoichiometric amounts, nor that even a majority of either species be complexed or bound to the other. All that is required is that a sufficient amount of an antigenic combination of the two species be presented in order to be able to stimulate an immune response there against."

Voss et al. discloses a vaccine composed of recombinant human immunodeficiency virus type 1 (HIV-1) gp120, Nef-Tat fusion protein, and simian immunodeficiency virus (SIV) Nef (see abstract). In accordance with the teaching in the specification, Voss et al. discloses a combination of the two proteins. Thus, Voss et al. anticipates the claimed invention.

Response to Arguments

In the reply dated October 13 2009, applicant argues that Tat and Env do not form a complex unless the V3 loop is exposed, and this does not occur with simple mixtures of Tat and Env/gp120. Applicant's arguments have been fully considered but not found persuasive.

The claims are directed to:

i) a first peptide comprising the V3 loop of gp120 (Voss et al. teaches gp120, which comprises V3).

ii) a second peptide comprising at least residues 21-40 and 46-58 of Tat (Voss et al. teaches the whole Tat protein, which comprising at least residues 21-40 and 46-58 of Tat). The structural components of the instant claims have been met by Voss et al. The claims are further directed to a complex where the first peptide is bound to the second peptide (V3 of gp120 binds to a binding region on Tat). There is no description of this bond (chemical vs physical). According to the specification, the two proteins associate with each other (see page 5, 4th paragraph).

The instant claims encompass gp120 and full length Tat forming a complex. Both gp120 and Tat are taught by Voss et al. in a mixture. Therefore, the proteins of Voss et al. also will bind to or associate with each other and form a complex.

Applicants next argue that none of the cited references teach the necessity for the accessibility of the V3 loop nor do any of the references teach conditions which would make the V3 loop available for binding to Tat. It is noted that the claims do not recite such limitations.

Claims 35-42, 45, 50-52, 63 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Debrus et al. (WO 02/087614).

Debrus et al. discloses a vaccine composed of HIV-1 gp120 and Nef-Tat fusions or Nef and Tat. Debrus et al. teaches that the gp120 protein is the principal target of neutralizing antibodies, but unfortunately the most immunogenic regions of the proteins (V3 loop) are also the most variable parts of the protein. Therefore, the use of gp120 (or its precursor gp160) alone as a vaccine antigen to elicit neutralizing antibodies is thought to be of limited use for a broadly protective vaccine. The gp120 protein does also contain epitopes that are recognized by cytotoxic T lymphocytes (CTL). For this reason gp120 and gp160 are considered to be useful antigenic components in vaccines that aim at eliciting cell-mediated immune responses (particularly CTL). Non-envelope proteins of HIV-1 have been described and include for example internal structural proteins such as the products of the gag and pol genes and, other non-structural proteins such as Rev, Nef, Vif and Tat (see pages 1 and 2).

Debrus et al. also teaches preferred combinations of adjuvant and antigen comprise the HIV gp120 and Nef-Tat proteins in combination with QS2 1,3D-MPL in an oil in water emulsion and that the proteins can be cross-linked. Preferably the Tat, Nef or Nef-Tat act in synergy with gp120 in the treatment or prevention of HIV (see pages 14 and 17).

In accordance with the teaching in the specification, Debrus et al. discloses a combination of the two HIV proteins. Thus, Debrus et al. anticipates the claimed invention.

Response to Arguments

In the reply dated October 13 2009, applicant argues that Tat and Env do not form a complex unless the V3 loop is exposed, and this does not occur with simple mixtures of Tat and Env/gp120. Applicant's arguments have been fully considered but not found persuasive.

The claims are directed to:

i) a first peptide comprising the V3 loop of gp120 (Debrus et al. teaches gp120, which comprises V3).

ii) a second peptide comprising at least residues 21-40 and 46-58 of Tat (Debrus et al. teaches the whole Tat protein, which comprising at least residues 21-40 and 46-58 of Tat). The structural components of the instant claims have been met by Debrus et al. The claims are further directed to a complex where the first peptide is bound to the second peptide (V3 of gp120 binds to a binding region on Tat). There is no description

of this bond (chemical vs physical). According to the specification, the two proteins associate with each other (see page 5, 4th paragraph).

The instant claims encompass gp120 and full length Tat forming a complex. Both gp120 and Tat are taught by Debrus et al. in a mixture. Therefore, the proteins of Voss et al. also will bind to or associate with each other and form a complex.

Applicant next argues that Debrus et al. teaches HIV antigens in combination with an HSV or HPV antigen and that this is not the same as the claimed invention. It is noted that the claims are directed to a complex "comprising" gp120 and Tat. Thus, because the open language "comprising" is used to describe the complex, other components such as HSV or HPV antigens can be present.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 41, 43, 44, 46-49 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voss et al. (WO 01/54719) or Voss et al. (Journal of Virology, 2003, 77(2):1049-1058) as applied to claim 35 above and further in view of Gzyl et al. (Virology, 2004, 318:493-506), Wyatt et al. (Journal of Virology, 1995, 69:5723-5733), Sattentau et al. (Journal of Virology, 1993, 67(12):7383-7393), Ibrahim et al. (Virus

Research, 1999, 60:159-169) and Watanabe et al. (Vaccine, 2000, 19(9-10):1199-1203).

The teachings of both references are outlined above. Neither reference teaches the use of the V3 loop, V2 deletion mutants, adding CD4 to the complex, adding heparin sulphate to the complex or cross-linking the peptides.

It is well known in the art that the V3 loop is one of the most immunogenic peptides of gp120. Thus, it would have been obvious to one of ordinary skill in the art to produce the vaccine composition of Voss et al. or Voss et al. using Tat and the V3 loop of HIV gp120. It also would have been obvious to cross-link the gp120 and Tat as cross-linking of vaccine antigens is common (see, for example, Watanabe et al.).

Gzyl et al. discloses Env peptides with increased immunogenicity. One Env peptide comprised a deletion of the V1 and V2 variable domains and a modification of the V3 loop (AV1/V2/mV3). This modified Env produced some of the highest level of cross-reactive responses (page 497). Wyatt et al. discloses involvement of the V1/V2 variable loop structure in the exposure of gp120 epitopes induced by CD4 binding. Wyatt et al. considers that the V2 loop is especially involved in partially masking epitopes on the native gp120 monomer.

Thus, based on the teachings of Gzyl et al. and Wyatt et al., it would have been obvious to one of ordinary skill in the art to create V2 deletions in the Env of Voss et al. or Voss et al. One would have been motivated and there would have been a reasonable expectation of success given the findings of Gzyl et al. (ΔV1/V2 mutant

produced a high level of cross-reactive immune responses) and Wyatt et al. (V2 loop masks epitopes of gp120).

Sattentau et al. discloses the use of soluble CD4 (sCD4) to induce conformational changes in the envelope glycoproteins of cell line-adapted isolates of HIV-1. Such sCD4-induced conformational changes have been detected on virions and include the dissociation of the SU glycoprotein, gp120, from the transmembrane (TM) glycoprotein, gp41, the increased exposure of the gp120/V3 loop demonstrated by greater cleavage of this loop by an exogenous proteinase, and stronger staining of gp41 with a monoclonal antibody (MAb) (see introduction). Ibrahim et al. teaches that heparin sulfates facilitate the binding of HIV-1 to cells.

Thus, based on the teachings of Sattentau et al. and the knowledge that the V3 loop is one of the most immunogenic peptides of gp120, it would have been obvious to one of ordinary skill in the art to include components, such as CD4 or heparan sulphate or other similar acting components/receptors, that would further expose the immunogenic peptides of V3 or facilitate the binding of gp120 to aid in, for example, generating CTL responses against HIV.

Response to Arguments

In the reply dated October 13 2009, applicant argues that none of the cited references teach the necessity for the accessibility of the V3 loop nor do any of the references teach conditions which would make the V3 loop available for binding to Tat. It is noted that the claims do not recite such limitations.

Claims 43, 44 and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debrus et al. (WO 02/087614) as applied to claim 35 above and further in view of Gzyl et al. (Virology, 2004, 318:493-506), Wyatt et al. (Journal of Virology, 1995, 69:5723-5733), Sattentau et al. (Journal of Virology, 1993, 67(12):7383-7393), and Ibrahim et al. (Virus Research, 1999, 60:159-169).

The teachings of Debrus et al. are outlined above. Debrus et al. does not teach V2 deletion mutants, adding CD4 to the complex or adding heparin sulphate to the complex.

Gzyl et al. discloses Env peptides with increased immunogenicity. One Env peptide comprised a deletion of the V1 and V2 variable domains and a modification of the V3 loop (AV1/V2/mV3). This modified Env produced some of the highest level of cross-reactive responses (page 497). Wyatt et al. discloses involvement of the V1/V2 variable loop structure in the exposure of gp120 epitopes induced by CD4 binding. Wyatt et al. considers that the V2 loop is especially involved in partially masking epitopes on the native gp120 monomer.

Thus, based on the teachings of Gzyl et al. and Wyatt et al., it would have been obvious to one of ordinary skill in the art to create V2 deletions in the Env of Debrus et al. One would have been motivated and there would have been a reasonable expectation of success given the findings of Gzyl et al. (ΔV1/V2 mutant produced a high level of cross-reactive immune responses) and Wyatt et al. (V2 loop masks epitopes of gp120).

Sattentau et al. discloses the use of soluble CD4 (sCD4) to induce conformational changes in the envelope glycoproteins of cell line-adapted isolates of HIV-1. Such sCD4-induced conformational changes have been detected on virions and include the dissociation of the SU glycoprotein, gp120, from the transmembrane (TM) glycoprotein, gp41, the increased exposure of the gp120/V3 loop demonstrated by greater cleavage of this loop by an exogenous proteinase, and stronger staining of gp41 with a monoclonal antibody (MAb) (see introduction). Ibrahim et al. teaches that heparin sulfates facilitate the binding of HIV-1 to cells.

Thus, based on the teachings of Sattentau et al. and the knowledge that the V3 loop is one of the most immunogenic peptides of gp120, it would have been obvious to one of ordinary skill in the art to include components, such as CD4 or heparan sulphate or other similar acting components, that would further expose the immunogenic peptides of V3 or facilitate the binding of gp120 to aid in, for example, generating CTL responses against HIV.

Response to Arguments

In the reply dated October 13 2009, applicant again argues that none of the cited references teach the necessity for the accessibility of the V3 loop nor do any of the references teach conditions which would make the V3 loop available for binding to Tat. It is noted that the claims do not recite such limitations.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571) 272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648